DETAILED ACTION

As indicated in the attached Interview Summary, Mr. Nathan Cassell called the Examiner on February 5, 2007, asking the status of claim 30, as claim 30 was not rejected in the Office Action of January 28, 2007. The following Office Action is a Supplemental Office Action, with claim 30 rejected under 103(a) as being obvious over Roth et al., US Patent 5,747,469, patented May 5, 1998, in view of De Brabander et al., 1981, PNAS, USA, 78: 5608-5612, in view of Rowinsky et al., 1995, The New England Journal of Medicine, 332: 1004-1014, in view of Santoso et al., 1995, Gynecologic Oncology, 59: 171-178.

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Claims 2, 6-9, 23, 24, 29, 33, 41-77 are cancelled. Claims 30, 80 are amended.

Applicant indicates that claims 37-40 were indicated as "rejected" in the Office Action of September 19, 2007. However, the Office Action of March 26, 2007 had indicated the claims as allowable and it is noted that no rejections were of record regarding these claims. In response, claims 37-40 were indicated as allowable, March 26, 2007. However, claims 37-40 and 79 have been newly rejected, see below, and are no longer considered allowable.

Claims 1, 3-5, 10-22, 25-28, 30-32, 34-40, 78-80 are under consideration.

Comment [a1]: don't put this in the present tense. you need to say that these claims WERE indicated as allowable in the previous office action. then make the "however" statement that claims 37 and 79 have been newly rejected below and are no longer considered allowable.

Comment [a2]: include all the active claims here, including ones objected to or considered allowable because until you send out a notice of allowance, the claims are still in play.

Withdrawn Rejections

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see page 8 of Applicant's response, filed October 31, 2007, with respect to the rejection of claim 30 as being indefinite have been fully considered and are persuasive. Applicant has amended claim 30 such that the adenoviral vector comprising a nucleic acid sequence encoding p53 is administered directly to ovarian cancer cells. The rejection of claim 30 has been withdrawn.

35 U.S.C. § 102(e)

Applicant's arguments, see page 9 of Applicant's response, filed October 31, 2007, with respect to the rejection of claims 1, 3, 10, 18-22, 25-28, 31, 32, 78, 80 as being anticipated by Tocque, US Patent 6,262,032 have been fully considered and are persuasive. Applicant indicates that US Provisional Application 60/038,065, filed February 18, 1997 has support for in vivo embodiments, page 28, line 22 to page 30, line 20. The rejection of claims 1, 3, 10, 18-22, 25-28, 31, 32, 78, 80 has been withdrawn.

35 U.S.C. § 103(a)

Applicant's arguments, see page 9 of Applicant's response, filed October 31, 2007, with respect to the rejection of claims 1, 10-17, 34 as being obvious over Tocque US Patent 6,262,032 in view of Gregory, US Patent 5,932,210 have been fully considered and are persuasive. Applicant indicates that Tocque is not a proper 102(e) reference and does not support the 103

Comment [a3]: Indicate why- the date does work, isn't that it?

rejection. In response, this is persuasive because Application 60/038,065, filed February 18, 1997 contemplated in vivo treatment, see page 28, line 22 to page 30, line 20. Applicant also indicates Gregory was owned or subject to an obligation of assignment to Canji, Inc. The rejection of claims 1, 10-17, 34 has been withdrawn.

Applicant's arguments, see page 10 of Applicant's response, filed October 31, 2007, with respect to the rejection of claims 1, 4, 5 as being obvious over Tocque US Patent 6,262,032 in view of Roth et al., 1997 have been fully considered and are persuasive. Applicant indicates that Tocque is not a proper 102(e) reference. In response, as indicated above, Applicant has contemplated in vivo treatment on page 28, line 22 to page 30, line 20 in 60/038,065. The rejection of claims 1, 4, 5 has been withdrawn.

Maintained/New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 80 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) an *in vivo* method for reducing the size of a tumor in a mammal comprising mammalian cancer cells deficient in functional p53, said method comprising directly contacting cancer cells with an adenoviral vector comprising a nucleic acid encoding p53, and also contacting said cells with a microtubule affecting agent, wherein the microtubule affecting agent

comprises a taxane, such that growth of said cancer cells is reduced and/or said cancer cells undergo apoptosis,

does not reasonably provide enablement for

1) an *in vivo* method of treating mammalian cancer cells deficient in functional p53, wherein said method comprises contacting cancer cells with an adenoviral vector comprising a nucleic acid encoding p53, wherein said vector is administered directly, and contacting said cells with a taxane, such that one or more disease characteristic of the cells is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, December 5, 2005 and July 5, 2006, March 26, 2007, September 9, 2007.

Applicant's arguments filed October 31, 2007 have been fully considered but they are not persuasive.

Applicant indicates that claim 80 has been amended such that the cancer tumor cells form part of a tumor. In response, this is not persuasive because claim 80 reads that "one or more disease characteristic of the cancer tumor cells is ameliorated," and is readable on treatment of metastatic cancer. Applicant's amendment indicates where tumor cancer cells can be found; however, the newly added phrase does not eliminate that the claim is readable on treatment of metastases.

Thus, the claims remains rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 10, 18-22, 25-28, 31, 32, 78-80 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Tocque, WO 96/22101, published July 25, 1996.

It is noted that Tocque, US Patent 6,262,032 is a 371 of this WO document and it is assumed that the 371 is an English translation of the WO document. It is also noted that since the disclosure is the same, the grounds of rejection are the same as that set forth in the Office Action, March 26, 2007. The rejection is copied here for Applicant's convenience, using the citations from the US Patent.

Tocque teaches a method of destroying a hyperproliferative cell in a tumor of an animal comprising administering a transgene construct comprising a nucleic acid sequence encoding p53 and a chemotherapeutic agent. Tocque teach H460 cells were transfected *in vitro* with a cDNA coding for the wild-type p53 protein placed in a plasmid under the control of a CMV promoter and were further treated with taxotere (Tocque, Example 3). Tocque teaches that the treatment with the p53 vector and taxotere reduce the number of H460 colonies more than by a treatment with taxotere only (Tocque, Fig. 3B). Further, Tocque also teaches that Example 3 demonstrates that cells treated with p53 vector and taxotere die at concentrations which are ineffective on cells that do not express wild-type p53 (Tocque, col., 7, 5th parag.). While Tocque teach one type of cells, Tocque contemplates that that the method is applied to cancer cells from

a variety of tissues, including colon, thyroid, and myeloid leukaemias (Tocque, col. 4, 6th parag.). Tocque teaches that the vector comprising a nucleic acid sequence encoding p53 and a taxane can be administered *in vivo* by intratumoral injection and that in order to obtain a maximum expression in a maximum number of dividing cells, administration of the transgene is repeated (Tocque, col. 13, parag. under "Administration Protocol", see also claims). In addition to plasmid, Tocque teaches the use of adenoviral vector (Tocque, col. 10, lines, 41-42, also see claims).

Tocque teaches that the nucleic acid vector is in an injectable form and thus is in a vehicle which is pharmaceutically acceptable for injection (Tocque, col. 4, 1st parag.). Tocque teaches that the two agents (nucleic acid vector and chemotherapeutic agent) may be used simultaneously, separately, or spread over time (Tocque, col. 4, 3rd parag.).

Regarding the administration of the chemotherapeutic agent (e.g. taxol), Tocque teaches that the chemotherapeutic agent is administered according to the clinical protocols in force (Tocque, col., 13, under Administration Protocol). According to Brown et al., taxol can be administered intravenously (Brown et al., see title and abstract). As such, Tocque has support for intravenous administration of taxol.

Thus, Tocque anticipate claims 1, 3, 10, 18-22, 25-28, 31, 32, 78-80.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 10, 18-22, 25-28, 31, 32, 34-40, 78-80 are newly rejected under 35 U.S.C. 103(a) as being obvious over Roth et al., US Patent 5,747,469, patented May 5, 1998, in view of De Brabander et al., 1981, PNAS, USA, 78: 5608-5612, in view of Rowinsky et al., 1995, The New England Journal of Medicine, 332: 1004-1014, in view of Dowsett et al., 1987, Cancer Research 47: 1957-1961.

Roth et al. teach a method of killing malignant cells by contacting said cells with a p53 gene and one or more DNA damaging agents in a combined amount effective to kill the cell(s) (Roth et al., col., 3, 3rd parag. under "Summary of the Invention"). Roth et al. teach that one common lesion in human cancers is mutation of p53 (Roth et al., col., 14, 1st parag. under "B. p53 and p53 Mutations in Cancer"). With regard to the expression of p53 in cancer cells, Roth et al. teach an adenoviral vector that expresses wild type p53 under the control of the human cytomegalovirus promoter (Roth et al., col. 17, 1st parag. under "E. p53-Adenovirus Constructs and Tumor Suppression"). With regard to DNA damaging agents, Roth et al. teach that agents that damage DNA include compounds that interfere with DNA replication, mitosis, and chromosomal segregation. Examples of these include adriamycin (also known as doxyrubicin), etoposide, verapamil, podophyllotoxin (Roth et al., col. 19, 3rd parag.).

While Roth et al. provide examples of compounds that interfere with DNA replication, mitosis and chromosomal segregation, Roth et al. do not teach taxol.

De Brabander et al., teach that taxol is a potent promoter of microtubule polymerization and induces massive assembly of free microtubules. Cells treated with taxol are blocked in the

G2 and M phases of the cell cycle (De Brabander et al., abstract and page 5608, 1st col., 1st parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use taxol as an agent that interferes with DNA replication, mitosis, and chromosomal segregation.

One having ordinary skill in the art would have been motivated to use taxol because Roth et al. teaches that a DNA damaging agent, such as a compound that interferes with DNA replication, mitosis, and chromosomal segregation, in combination with an adenoviral vector that expresses wild type 53, can be used to kill cancer cells.

There would have been a reasonable expectation of success given that Roth et al. teach the combination of p53-adenovirus and a DNA damaging compound can be used to treat cancer.

With regard to the claims being drawn to "paclitaxel," (e.g. see claim 3) it is noted that paclitaxel is the same as taxol (see Rowinsky et al.).

With regard to the claims being drawn to an additional chemotherapeutic agent (claims 4, 5), Roth et al. teach that their method uses one or more DNA damaging agents (Roth et al., col. 3, lines 64-65). Cisplatin is envisioned to be a DNA damaging agent that can be used (Roth et al., col., 4, lines 64-65).

With regard to the claims being drawn to the order in which p53-adenovirus and taxol are administered (claims 20-22), Roth et al. teach that the target cell may be first exposed to the DNA damaging agent (i.e.,taxol) and then with the p53-adenovirus (or vice versa). Also, the p53-adenovirus can be administered simultaneously with the DNA damaging agent (Roth et al., col. 4, 2nd and 3rd parags.).

With regard to the claims being drawn to putting the p53-adenovirus and taxol, each into an excipient, or both into one excipient (claims 25-27), Roth et al. teach both types of formulations can be carried out (Roth et al., col. 4, 2nd parag.).

With regard to route of administration (claims 28, 31, 32), Roth et al. teach that p53-adenovirus be injected into the tumor (Roth et al., col., 7, 6th parag.). It is noted that Roth et al. also envision that p53-adenovirus and taxol can be formulated to be administered together; as such, this addresses taxol being directly applied to the tumor (claim 31). As for administration of taxol, Rowinsky et al. teach that taxol can be administered via i.v. (Rowinsky et al., page 1005, 2nd col., line 11; "infusions" of taxol).

With regard to the dosing regimens (claims 35-40), the frequency of administering a drug is part of routine optimization. By way of example, Dowsett et al. teach different routes of administration, different dosages, and different numbers of doses of 4-OHA to identify the minimal effective dose and optimal therapeutic regimen (Dowsett et al., abstract). Similarly, an artisan would have tried a variety of dosing regimens in order to determine the appropriate dosing regimen of adenoviral comprising the nucleic acid sequence of p53 and taxol.

With regard to the amount of adenoviral vector and taxol (claim 37), Roth et al. teach administration of $1x10^5$ to $1x10^{12}$ pfu of virus (Roth et al., claim 16) and Rowinsky et al. teach patients who were being treated for ovarian cancer received 110 to 135 mg per square centimeter of paclitaxel (Rowinsky et al., page 1009, 1st col., 1st parag., line 3) and patients being treated for lung cancer received 200 to 250 mg per square meter (Rowinsky et al., page 1011, 1st col., 1st parag. under "Lung Cancer"). It is noted that while Rowinsky et al. is not explicit as to how often taxol was administered, it is inferred that taxol is administered once. As such, the

teachings of Roth et al. and Rowinsky et al. meet the limitation of claim 37 with regard to "total dose in a single dose".

Claims 1, 3-5, 10, 18-22, 25-28, 30-32, 78-80 are newly rejected under 35 U.S.C. 103(a) as being obvious over Roth et al., US Patent 5,747,469, patented May 5, 1998, in view of De Brabander et al., 1981, PNAS, USA, 78: 5608-5612, in view of Rowinsky et al., 1995, The New England Journal of Medicine, 332: 1004-1014, in view of Santoso et al., 1995, Gynecologic Oncology, 59: 171-178.

As discussed above, Roth et al., in view of De Brabander et al. teach an artisan to treat tumors by administering an adenoviral vector comprising a nucleic acid sequence encoding p53 and taxol. While Roth et al. and De Brabander et al. provide this teaching, they do not teach treatment of ovarian cancer.

Rowinsky et al. teach that taxol can be used to treat ovarian cancer (Rowinsky et al., page 1004, 1st col., 1st parag., line 9).

Santoso et al. teach adenoviral vector comprising a nucleic acid sequence encoding wild type p53 being administered to ovarian cancer cells (Santoso et al., abstract).

Roth et al. teach in vivo combination therapy for tumors using adenoviral vector comprising a nucleic acid sequence encoding wild type p53 and taxol. Roth does not specifically indicate that ovarian cancer be treated. Rowinsky et al. and Santoso et al. each teach that taxol and adenoviral vector comprising a nucleic acid encoding wild type p53 can be used to treat ovarian cancer.

All of the known components of treating ovarian cancer were taught in Roth et al., Rowinsky et al., and Santoso et al. The only difference is the combination of adenoviral vector comprising a nucleic acid sequence encoding wild type p53, taxol, and treatment of ovarian cancer.

It would have been obvious to one having ordinary skill in the art to use the combination therapy of Roth et al. to treat ovarian cancer since the Rowinsky et al. and Santoso et al. teach that ovarian cancer was being treated by adenoviral vector comprising a nucleic acid sequence encoding wild type p53 and taxol.

Claims 1, 3, 10-13, 15-17, 34 are newly rejected under 35 U.S.C. 103(a) as being obvious over Roth et al. US Patent 5,747,469, patented May 5, 1998, in view of De Brabander et al., 1981, PNAS, USA, 78: 5608-5612, in view of Wills et al., 1994, Human Gene Therapy, 5: 1079, see PTO-892, December 5, 2005.

As discussed above, Roth et al. in view of De Brabander et al. teach an artisan to treat tumors by administering an adenoviral vector comprising a nucleic acid sequence encoding p53 and taxol. While Roth et al. and De Brabander et al. provide this teaching, they do not teach ACN53.

Wills et al. teach ACN53, an adenoviral vector that comprises a nucleic acid sequence encoding wild type p53. Wills et al. teach that the p53 adenoviral construct are based on Ad 5 and have had the E1 region of nucleotides 360-3325 replaced with a 1.4-kb full length p53 cDNA sequence driven by a CMV promoter, followed by the Ad 2 tripartite leader cDNA. The E1b sequence, protein IX, and the E3 region was also deleted in the construct (Wills et al.,

Figure 1). Wills teach that injection of a tumor with ACN53 results in suppression of tumor growth and increased survival time of the tumor model.

Roth et al. teach that adenoviral constructs comprising a nucleic acid sequence encoding wild type p53 can be used to treat tumors. However, Roth et al. do not teach ACN53. Wills et al. teach ACN53 is an adenoviral vector that can be used to treat tumors. Because both Roth et al. and Wills et al. teach treatment of cancer using adenoviral constructs comprising a nucleic acid sequence encoding wild type p53, it would have been obvious to one skilled in the art to substitute a general adenoviral vector comprising a nucleic acid sequence encoding p53 taught by Roth et al. with the particular one, ACN53, taught by Wills et al.

Claims 1, 10, 11, 14 are newly rejected under 35 U.S.C. 103(a) as being obvious over Roth et al. US Patent 5,747,469, patented May 5, 1998, in view of De Brabander et al., 1981, PNAS, USA, 78: 5608-5612, in view of Wills et al., 1994, Human Gene Therapy, 5: 1079, see PTO-892, December 5, 2005, in view of Krougliak et al., 1995, Human Gene Therapy, 6: 1575-1586.

As discussed above, Roth et al., in view of De Brabander et al., in view of Wills et al. teach an artisan to treat tumors using ACN53 and taxol. However, none of the references teach deletion of adenovirus early region 4 in the adenoviral vector.

Krougliak et al. teach that an adenoviral vector comprising a deletion of E1, E3, and E4 is more severely attenuated that vectors that have deletions only in E1 or E1 and E3, and are thus safer in gene therapy protocols.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make an adenoviral vector with a deletion in E4.

One having ordinary skill in the art would have been motivated to make a deletion in E4 of an adenoviral vector because Krougliak et al. teach that adenoviral vectors that have deletions in E1, E3, and E4 are safer than those with either E1 or E1 and E3 deletions.

There would have been a reasonable expectation of success given that Krougliak et al. teach that adenoviral vectors can be used in gene therapy applications and that deletion of E1, E3, and E4 would result in a vector that is safer than E1 or E1 and E3-deleted vectors.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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